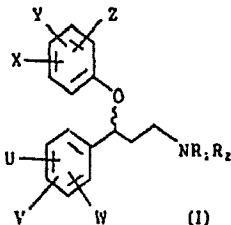


92-398487/48 B05 UYPE- 91.05.01
UNIV PENNSYLVANIA *WO 9219210-A2
91.05.01 91US-694346 (92.11.12) A61K
Novel serotonin re-uptake inhibitor cpds. are antidepressants, also useful for imaging serotonin receptors when contg. radioactive halogen isotopes (Eng)
C92-176712 N(CA JP) R(AT BE CH DE DK ES FR GB GR IT LU MC NL SE);
Addnl. Data: KUNG H F
92.04.22 92WO-US03261

Substd. 3-phenoxy-3-phenylpropylamine derivs. of formula (I) and their salts are new:



B(5-A3A, 5-A3B, 5-B1B, 7-H, 10-A4, 10-A8, 10-A10, 10-A13D, 10-A15, 10-A18, 10-A19, 10-B1A, 10-B2B, 11-C7B5, 12-C10, 12-G1, 12-K4A5)
U, V, W, X, Y, Z = H, halo or 1-4C alkyl or 1-4C alkoxy (both opt. substd. by halo and/or OH), 1-6C heterocycle, 1-4C thioalkyl, NR₁R₂, -R₃-A-R₄, -A-R₇, CN, SO₂R₈, NIICONH₂ or CONR₃R₄;
R₁-R₂ = H or 1-4C alkyl;
R₃, R₄ = 1-6C alkyl;
R₇ = H, 1-6C alkyl, 1-6C heterocycle or -A-R₅;
R₈ = 1-4C alkyl or NR₃R₄;
A = S, NH or O;
provided that at least one of U-Z = halo.

Intermediate cpds. of formula (II) (see "Preparation") are also new.

USE

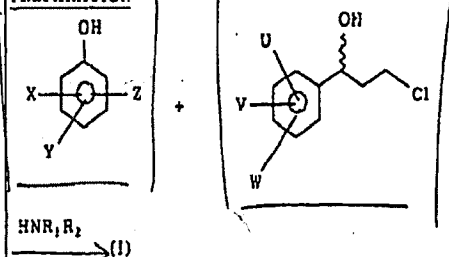
(I) bind to neurotransmitter reuptake sites and esp. inhibit serotonin reuptake. Radioactive halogen (esp. ¹²⁵I) labelled cpds. of (I) are useful for imaging serotonin receptors using single photon emission tomography (SPECT) to assess and improve treatment of psychiatric disorders. (I) may also be useful for in vitro binding studies and as therapeutic agents.

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SPECIFICALLY CLAIMED

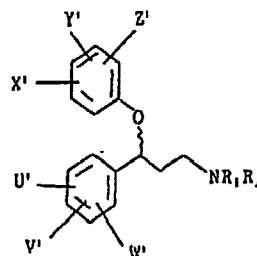
N-methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine (Ia).

PREPARATION



Radioactive I-labelled cpds. of (I) are prepd. by treating the corresp. Br-cpd. with Et₃N/tetrakis(triphenylphosphine) palladium, then stirring the resulting tributyltin deriv. (IIa) with I₂/CHCl₃ or NaI/H₂O₂(aq.).

Other intermediates within the scope of (II) may be used to prepare the radiolabelled cpds. in an analogous manner.



one of U', V', W', X', Y', Z' = Sn(R), Si(R), or HgR and the others are as defined for U-Z;
R = 1-5C alkyl.

EXAMPLE

A mixt. of (R)-(+)-1-chloro-3-phenyl-3-(4-iodo-2-methylphenoxy)propane (0.58 g), eq. MeNH₂ (40%, 4 ml)

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and EtOH (1.5 ml) was heated at 130°C for 3 hr. in a sealed tube and worked up to give 0.25 g (44%) (R)-(-)-(Ia) α²⁵_D = + 11.98 (c 3.32, CHCl₃); HCl salt had m.pt. 68°C, α²⁵_D = -8.34 (c 0.82, CHCl₃).

In in vitro competitive binding assays using rat brain tissue prepn. (Ia). HCl had Ki 5 nM (serotonin uptake, (³H-paroxetine)) and IC₅₀ 20 nM (norepinephrine uptake, (³H-nisoxetine). (26pp2218AFDwgNo0/3).

SR:No-SR.Pub

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